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13. ABSTRACT (Maximum 200 Words)

Most breast cancer cases in the Philippines present at advanced stages and have a rapid unfavorable outcome. Breast Clinical Examination (CBE) undertaken by health workers appears to be an attractive compromise with a good cost-effectiveness ratio suitable for a country with limited resources. We conducted an intervention study to assess the feasibility and efficacy of screening by CBE in reducing mortality from breast cancer. However, the sensitivity of the screening program in the real context is low. Moreover, despite high compliance with the examination, this intervention failed to improve compliance with clinical investigation.

The natural development of the lesson learnt from the screening project is the need to device sustainable programs that can overcome the barriers currently causing the delay of diagnosis and high fatality rates for a disease that is potentially curable even with limited resource.

The protocol of a demonstration project that aims to improve access to and quality of breast cancer care within the limits of the local health system is being developed. Key elements of the program include promoting collaboration between the referral cancer center and primary health units. The first will provide expert examiners and appropriate treatment regiments according to agreed guidelines. The second will promote early diagnosis in the resident population and ensure timely liaison with the cancer center. A monitoring system will be set up to measure progress.

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Introduction and background

In wealthy countries where breast cancer is the leading site of malignant neoplasms in women, mortality from the disease has been significantly reduced with mass screening by mammography combined with timely optimal treatment. Research on the causes of the disease has progressed producing evidence that established risk factors for cardiovascular and some metabolic diseases are also determinants of an increased risk of breast as well as other cancers. Such risk factors are linked to the affluent life-style that becomes quickly widespread in countries in economical transition such as the Philippines. Preventive interventions addressing such risk factors individually, e.g. excess body weight, are unlikely to be successful and to have a measurable impact on the incidence of breast cancer. Interventions of primary prevention should address multiple major risk factors and monitor multiple outcomes.

Mortality from breast cancer is declining in affluent countries thanks to early detection and appropriate management of the disease. Early diagnosis and access to optimal treatment should therefore be a priority for countries in economic transition where a continuing increase of breast cancer risk has been documented. Screening by mammography would require investments in terms of equipment, expertise and direct costs unaffordable even in a middle-income country, and is certainly not advisable. An alternative screening modality is Clinical Examination of the Breast (CBE) the value of which by as a means of reducing mortality from breast cancer (BC) is not established.

The aims of the original project were to assess whether mass screening by CBE performed by trained para-medical personnel is feasible in an urban population of a low-income country, and its efficacy in reducing BC mortality.

The study was designed as a randomised controlled trial of the effect on BC mortality of five annual CBE performed by trained nurses. The target population was women aged 35-64 years, resident in

12 municipalities of the National Capital Region of Manila, Philippines. The units of randomization were the 202 health centres (HCs) within the selected municipalities. During 1995 nurses and midwives were recruited and trained in performing CBE. The first round of screening took place in 1996-1997. The intervention however revealed a refractory attitude of the population with respect to clinical follow-up and was discontinued after the completion of the first screening round. Cases of breast cancer occurring in the study population during 1996-1999 were identified by the two local population-based registries.

In the single screening round 151,168 women were interviewed and offered CBE, 92% complied (138,392), 3479 were detected positive for a lump and referred for diagnosis. Of these only 1220 women (35%) completed diagnostic follow-up, while 42.4% actively refused further investigation even with home visits, and 22.5% were not traced. Of the 53 cases that occurred among screen-positive women only 34 were diagnosed through the intervention. Eighty cases occurred among screen-negative women. The actual sensitivity of the programme was 25.6% and positive predictive value 1%. Screen-detected cases were non-significantly less advanced than the others.

In conclusion. Previous studies have shown that most breast cancer cases in the Philippines present at advanced stages and have a rapid unfavorable outcome. Although CBE undertaken by health workers seems to offer a cost-effective approach to reducing mortality, the sensitivity of the screening program in the real context was low. Moreover, in this relatively well-educated population, cultural and logistic barriers to seeking diagnosis and treatment persist and need to be addressed before any screening program is introduced.

In this document, after the section reporting on last year activities, we describe a proposal of new research work to test the impact on a short-term of a redesigned organizational setting of health education and health care delivery compatible with the low resources available for the management of cancer and therefore sustainable also on large scale.

Report on activities from October 2003 to September 2004

The primary objective was to complete the analysis of the data already collected and pursue reporting on scientific peer reviewed journals.

The design of the study and core results of the screening intervention are being published on the International Journal of Cancer (annex 1).

A second manuscript on a study describing current practices of treatment for breast cancer in Manila has been submitted for publication (see annex). This study shows that the 900 breast cancer cases newly diagnosed every year in Manila are treated in over 100 hospitals and clinics in the urban area. Only half of the cases are concentrated in the three large governmental hospitals, the others are scattered among the numerous non-specialized existing clinics. There is not a cancer center in Manila.   Radiotherapy is rarely administered (though the necessary facilities exist) and systemic therapy, both chemo- and hormone therapies, are administered preferably to more advanced cases. The study documents that standard practices are sub-optimal and that resources could be optimized by reorganizing the health services involved.

This study was described in objectives B1 and B2 of 2003 report.

Other analyses are on-going. Progress and status are described below.

A. Studies of factors that influence the risk of BC in the female Filipino population:

A.1   A case-control study nested in the intervention cohort, based on the 123 cases identified by record linkage, and 8 times as many controls. Controls were randomly extracted from the intervention cohort members to match cases on age ($\pm$ 3 yrs), date when examined ($\pm$3 months) and municipality of residence. The objective is to quantify relative risks and attributable fractions in a population that

maintains several characteristics of low-risk developing countries but where incidence rates are as high as in Southern Europe.

Achievements:

The analysis is on-going. Interim results show no association between breast cancer and socio-economic level expressed by the average income per family member. On the contrary we observed a strong association with fertility: the incidence of breast cancer is 3 times greater in women with no children compared with women with 6 or more full-time pregnancies (RR=3.3, 95%cl 1.6-6.7). Their risk is even greater when compared with women who had their first child before age 19 (RR=4.8, 95%cl 1.8-13.2). We also observe clear dose-response relationships between parity and age at first child. These results are in agreement with the literature. The associations reported are particularly strong.

A.2   Descriptive study of factors associated with a positive family history of breast or ovarian cancer. Three thousand women (2% of the intervention cohort) reported a positive history of breast or ovarian cancer. They will be compared with a suitable sample of family-negatives to assess whether they differ in any of the risk factors for BC investigated.

Achievements: The family history of 2,912 women who reported a positive history of breast or ovarian cancer were computerized. Data checking and cleaning is on-going.

A.3   Descriptive study of determinants of migration outside the urban area.   We tried to contact 3000 women at their original address 2 years apart from interview. Almost half of them had moved out. We will evaluate whether their socio-demographic characteristics, as assessed by our questionnaire, would allow us to identify a stable subpopulation suitable for long-term follow-up.

Achievements: analysis on-going.

B.   Descriptive studies addressing quality of care and management of breast cancer in the urban area of Manila:

B.1 & B.2   <u>Trends in the frequency of advanced disease and patterns of treatment by stage, age and socio-economical level</u>. In 1995, before the intervention, over 75% of the breast cancers diagnosed in this population were stage III or worse. We will assess whether any significant improvement occurred by 1999.

The clinical history of incident cases in 1991, 1994 and 1997 was updated to February 2004 by reviewing medical records and, when these were insufficient, by direct contact of the treating doctors. The information was computerized and analyzed.

Achievements: analysis completed, manuscript submitted (see annex 1).

B.3   <u>Validity of BCE performed by the nurses in the intervention compared with doctors and clinical follow-up.</u> The nurses recorded the physical characteristics of the lumps that they diagnosed as they felt them. These will be compared with the same characteristics as reported by follow-up doctors.

Achievements:

The outcome of CBE recorded by the nurses examiners on *ad hoc* forms at time of the intervention was computerized. Each lump detected was identified by location (15 sectors of each breast), approximate size, hardness and mobility. For women who were confirmed as malignant cases, these data are being compared with the stage assessed at diagnosis. The characteristics of false positives are also described.

Body

Demonstration project: improving sustainable breast health care in a developing country

Based on cause-specific mortality The Philippines has reduced substantially most of the disease risks linked to poverty (e.g. malnutrition, infant mortality due to infections) although per capita total expenditure on health is 100 times lower than that of affluent countries (2).

All facilities for a timely diagnosis of breast cancer exist in the urban area of Manila. Surgery and systemic treatments are also widely available though delivery appears sub-optimal. The capacity of radiotherapy centers is the only resource insufficient to satisfy demand. Some limits in the infrastructures do not however explain the unfavorable distribution of stage at presentation and average patterns of breast care practices.   The experience of the randomized trial has highlighted serious barriers towards early diagnosis in the urban population of Manila despite knowledge of the neoplastic disease is widespread. Distrust with respect to treatment efficacy and low expectation towards the health system are the main reasons that prevent Filipino women from seeking medical attention.   There is a need to built cost-effective programs to deliver breast cancer care able to conquer the confidence of the population. A key requisite for early detection is that women are supported in seeking care and that they have access to appropriate, affordable diagnostic tests and treatment.   There is also the need to improve the quality of the diagnostic procedures and of the disease management through a more rational use of existing resources. This can be achieved by creating cancer centers that concentrate expertise and ensure homogeneity of treatment protocols. In order to improve access, experienced personnel of the health center will ensure regular breast clinics, e.g. on a monthly basis, in primary health centers.

CBE will be offered to women referring to Health Centers on days of Breast Clinic. The feasibility of combining CBE with ultrasound examination for the purpose of improving the triage of positive cases will be considered and tested. The efficacy of the new organizational settings will be assessed by several indicators: a) the rate of compliance with referral among women positive for a breast lump

either self-reported or detected at a screening examination offered in breast clinic days; the distribution of stage at diagnosis; c) the treatment regiment received in the first year and d) survival and incidence of disease recurrence.

The new organizational setting will involve minimum extra investments and will largely rely on existing resources. Access to health care should also be facilitated by the introduction of a health insurance system. In 1995, the Philippines government legislated to create an income-rated and predominantly employment-based universal health insurance program over a 15-year period. The program was intended to provide more and better health care than was available through a combination of existing insurance schemes that covered less than half of the population, and partially subsidised services provided by government facilities and funded from general taxation. Improvements in access to health followed the introduction of the program.

The natural development of the lesson learnt from the screening project is to device sustainable programs that can overcome the barriers currently causing the delay of diagnosis and high fatality rates for a disease that is potentially curable even with limited resource.

Work Plan October 2004 – September 2005.

Objective

We propose to devote the next contract year to develop the protocol of a demonstration project that aims to improve access to and quality of breast cancer care within the limits of the local health system. Key elements of the program include promoting collaboration between the referral cancer center and primary health units. The first will provide expert examiners and appropriate treatment regiments according to agreed guidelines. The second will promote early diagnosis in the resident population and ensure timely liaison with the cancer center. A monitoring system will be set up to measure progress.

Setting and logistics

The municipality of Pateros is the smallest of the 12 cities that participated in the screening project. It is divided in 5 Health Centers (HC) serving a population of 58,000 of which 10,400 women aged 35+ years. The municipality is served by the Rizal Medical Center, one of the three governmental hospitals that served as referral centers for diagnosis and treatment in the screening project. The Rizal Medical Center runs the population-based cancer registry of Rizal that covers the city of Pateros (3). In 2004 the RMC was equipped with a radiotherapy department.

A community-based intervention to reduce risk factors for cardiovascular diseases (CVD) has been recently implemented in Pateros by the Department of Health (DOH) of the Filipino Government in collaboration with the WHO Regional Office. The intervention follows the recognition of the high mortality from CVD and cancer together with increasing incidence of diabetes and hypertension (from cross-sectional surveys) and the high priority of measures for NCD prevention and control in the country.

The intervention addresses smoking cessation, healthy diet (increase vegetables and fruit, decrease salt intake), physical exercise and avoidance of overweight; height and weight are measured and

recorded and screening for hypertension, diabetes and impaired glucose tolerance are performed. Cervical cytology smears and clinical examination of the breasts are performed on request and in symptomatic women.

The CVD project design involves a baseline risk factor survey using the WHO STEPwise approach to NCD Surveillance, an opportunistic health promotion activity in the interim, with a repeat survey after three-four years.

The intervention is conducted by regular staff (nurses, midwives and doctors) of the 5 Health Centres (HC) of the municipality. Health promotion activities are added to routine workload. That means that the intervention applies only to walk-in patients. One day a week is devoted to screening and treatment for diabetes.

This project is at the very first step that involves setting up the infrastructures (training of existing personnel and logistics). The intervention is currently operative. The only planned evaluation of the clinical intervention for the time being consists in monitoring the prevalence of hypertensive and diabetic individuals over time. The association of these two disorders with incidence and mortality from CVD is so strong that they can be considered good outcome measures to evaluate the intervention.

A serious limitation of this activity is that it is limited to walk-in patients of the 5 health centres involved. There is no assessment at present of what this means with respect to population coverage and numbers of subjects actually reached by the intervention.

Moreover, a mechanism to monitor and evaluate the intervention has not been set up as yet. Only process parameters are being recorded.

No plan to evaluate the outcome of the down-staging activity has been set up as yet, nor of any possible impact on risk factors with respect to cancer incidence. Numbers would be too small to detect an impact for mortality that would also require long-term follow-up of the population.

The results of all tests and measures, either symptomatic or as opportunistic screening, are recorded on standard forms and filed in individual medical records maintained at the HCs.

The HCs also provide for regular updates of the resident population by household. This is a key element of the evaluation of any intervention since it permits to establish overall coverage and actual improvements in population access to health care.

Plan of Work

The activities planned for next contract year are:

1. computerise and analyse the outcome of opportunistic screening tests for CVD and cancer currently performed;

2. computerise population lists;

3. match and analyse those data in order to establish the current level of population coverage, and the prevalence of risk factors;

4. establish close collaboration between the RMC and the HCs in Pateros to ensure the regular provision of expertise in the peripheral centres;

5. set up a monitoring system that permits the evaluation of the actual compliance of patients with referral for diagnosis and treatment and to measure average delay time.

6. based on the above information, develop the detailed protocol of the demonstration project.

Ancillary studies

the high risk of BC in Filipino women among all Asian females remains unexplained in view of the still high reproductive rates. The screening tests for CVD and diabetes will also allow us to conduct cross-sectional studies on markers of insulin and glucose control, and on their association with breast

cancer and with established risk factors for the disease linked to women's reproductive history and body mass index. The objective of these studies is to establish if the prevalence of known risk factors in this population can justify the relatively high incidence to an extent consistent with what is known for Western populations.

Partners

The following institutions are involved in the development and implementation of the study:

- The Department of Health of the government of the Philippines, NCD Department, Drs F. Diza and F. Cuevas

- The Country Representative of WHO, Dr J.M. Olive

- The NCD Unit of the Regional Office for the Western Pacific of WHO, Dr G. Galea

- The Rizal Medical Center, Pasig City, Dr Maria-Rica Mirasol-Lumague

- The University of the Philippines, Institute of Public Health, Prof. Jane Baltazar.

Key research accomplishments

- Quality of breast cancer treatment and care in a developing country.

- Risk of breast cancer in relation to several characteristics of women's reproductive life, obesity, height, alcohol consumption, family history of breast cancer and tobacco smoking.

- Prevalence of risk factors for breast cancer in the female population of Metro Manila.

- The same factors above plus education and socio-economical level as determinants of stage at diagnosis of breast cancer and survival, taking account of treatment received.

- Determinants of compliance with early diagnosis and treatment in a developing country.

REPORTABLE OUTCOMES

- Poster presentation at the Era of Hope Conference, Washington D.C., 1-4 October 1997.

- Poster presentation at the Era of Hope Conference, Atlanta, 8-11 June 2000.

- Poster presentation at the second Era of Hope Conference, Orlando, 25-28 September 2002

- REC-LINK software program – for automatic matching of records based on personal id-items (e.g. name, surname, age, date of birth, address).

- Data base of the female population resident in Metro Manila in years 1995-1996.

- Data base of new cancer cases diagnosed in the resident population 1990-2001.

- Data base of incident breast cancer cases, years 1995-2001, with clinical details of stage at diagnosis and initial treatment.

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Outcome of screening by clinical examination of the breast in a trial in the Philippines

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Running title: Breast cancer screening by clinical examination.

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Abstract

Background. The value of screening by Clinical Examination of the Breast (CBE) as a means of reducing mortality from breast cancer (BC) is not established. The issue is relevant, as CBE may be a suitable option for countries in economic transition, where incidence rates are on the increase but limited resources do not permit screening by mammography. The aims were to assess whether mass screening by CBE performed by trained para-medical personnel is feasible in an urban population of a low-income country, and its efficacy in reducing BC mortality.

Methods. The study was designed as a randomised controlled trial of the effect on BC mortality of five annual CBE performed by trained nurses. The target population was women aged 35-64 years, resident in 12 municipalities of the National Capital Region of Manila, Philippines. The units of randomization were the 202 health centres (HCs) within the selected municipalities. During 1995 nurses and midwives were recruited and trained in performing CBE. The first round of screening took place in 1996-1997. The intervention however revealed a refractory attitude of the population with respect to clinical follow-up and was discontinued after the completion of the first screening round. Cases of breast cancer occurring in the study population during 1996-1999 were identified by the two local population-based registries.

Results. In the single screening round 151,168 women were interviewed and offered CBE, 92% complied (138,392), 3479 were detected positive for a lump and referred for diagnosis. Of these only 1220 women (35%) completed diagnostic follow-up, while 42.4% actively refused further

investigation even with home visits, and 22.5% were not traced. Of the 53 cases that occurred among screen-positive women only 34 were diagnosed through the intervention. Eighty cases occurred among screen-negative women. The actual sensitivity of the programme was 25.6% and positive predictive value 1%. Screen-detected cases were non-significantly less advanced than the others.

Conclusion. Previous studies have shown that most breast cancer cases in the Philippines present at advanced stages and have a rapid unfavourable outcome. Although CBE undertaken by health workers seems to offer a cost-effective approach to reducing mortality, the sensitivity of the screening programme in the real context was low. Moreover, in this relatively well-educated population, cultural and logistic barriers to seeking diagnosis and treatment persist and need to be addressed before any screening programme is introduced.

Introduction

In the year 2000 breast cancer accounted for over 1 million new cases per year worldwide; it is the most common cancer in women, and incidence rates are rising in low-risk countries[1]. These trends are likely to continue, since the current pattern of later childbearing, decreasing fertility, increasing height and weight and 'westernization' of diets will all be associated with increased risk.

Significant improvements in the prognosis of early breast cancer have been achieved in the 80s and 90s[2,3] and have substantially contributed to the initial reduction of mortality observed in some high-risk countries[4, 5, 6, 7]. For treatment to be highly effective however, it is essential that the disease is detected at an early clinical stage.

Possibly because of the low burden relative to other diseases, cancer awareness in low-risk developing countries is generally poor. Cases tend to present at an advanced stage and have an unfavourable outcome. This may induce a general sort of pessimism in the medical community about the capacity of the health system to impact on cancer prognosis even for sites that can be successfully treated. Such pessimism is not justified since even when resources are limited at least 60% of breast cancer cases presenting with disease localised to the breast survive 5 years from diagnosis [8]. A shift towards a more favourable distribution of stage would therefore have a measurable impact on mortality.

We planned this study to test the feasibility and the effect of systematic screening of the population by clinical breast examination (CBE) on stage at presentation and ultimately on breast cancer mortality, in the urban area of Manila, the Philippines, where the two local cancer registries had reported over 60% of the cases were at stage III or VI at diagnosis[8]. The study was designed as a randomised trial and was planned to involve 5 rounds of screening for women in the intervention group, at intervals of 1-2 years.

In this manuscript we describe the study population, the intervention and its results in terms of breast cancer detection, cumulative incidence in 3 years of follow-up in the group examined and in control areas and sensitivity and specificity of the examination in that setting. However, due to a very low compliance with clinical follow-up the intervention ceased after completion of the first round of examinations. We discuss reasons for the outcome and implications for the development of cancer control plans in developing countries.

Materials and methods

Study design. The study began in 1995. It was designed as a randomised controlled trial of the efficacy of five annual clinical examinations of the breasts performed by trained nurses/midwives, in reducing mortality from breast cancer. Women aged 35-64 years, resident in the 12 central, more urbanized municipalities of the National Capital Region of Manila were the target population. Young women were included because of the high proportion of cases below age 50[9]. In 1990, the estimated size of the female population aged 35-64 was about 340,000. The units of randomization were 202 health centres (HCs) within the selected municipalities. These were randomly assigned to intervention or control arm by block randomization. Blocks were defined based on population size and a deprivation index indicating the presence of squatters areas within the administrative borders.

Identification of the eligible population. Lists of women resident in the 12 municipalities and who were included in the electoral rolls were obtained from the Department Of Health (DOH). Women were identified by family and first name, date of birth and complete address (street and administrative area which coincided with the area served by a health centre). Electoral rolls had last been updated in during 1994-95.

Intervention. In the first year (1995) a coordinating centre was set up. Nurses and midwives were recruited and trained in the technique of CBE using the MAMMACARE ™ [10] programme previously tested in the Philippines, that uses silicone models of the breast for training purposes[11] and has been shown to enhance performance of examiners in previous studies[12,13,14].

Training was repeated for selected groups of examiners who missed or over-reported by 20% the lumps in the silicon models.

The first round of examinations took place in 1996-1997 (24 months) and included 151,168 women. Eligible women resident in the intervention HCs were contacted in two ways: at the HC among those women who were attending for a variety of reasons, and, for those who did not, by systematic home visits. Basic demographic characteristics (age, marital status, socio-economic level) of eligible women were recorded and the nature and purpose of the intervention were explained. Women were asked to give a signed assent to participation. They were interviewed, and CBE was carried out by the trained examiners. The interview addressed socio-demographic variables and classical risk factors for breast cancer. Women were also instructed in the technique of breast self-examination (BSE) and provided with a leaflet in the local language explaining the purpose and methodology of BSE.

Women in whom abnormalities were detected and classified "positive" for a suspected lump were referred for diagnosis to special clinics established in 3 major hospitals and staffed by project personnel. The costs of transport to the clinic and of all medical procedures required to reach diagnosis were covered by the project. In addition, in the last year of the intervention period, a mobile team, comprising a doctor and a nurse and equipped to perform needle biopsies, carried out home visits for all positive women who had not reported to the referral centre, in order to obtain a final diagnosis. The diagnostic standard process consisted in a physical examination by a specialist doctor followed by fine needle or excision biopsy if indicated. Mammography was not available to the large majority of the women judged positive.

Women in the control area received no active intervention but were exposed to the general health education campaigns carried out by municipal authorities and voluntary bodies.

Follow-up. The aim of the follow-up of the intervention and control cohorts was to identify women who developed breast and/or other cancers, those who died and those who migrated outside the study area.

Two cancer registries, Manila-PCS and Rizal-DOH[9], covered the study population. Together they serve the whole metropolitan area and the surrounding more rural province of Rizal. The case-finding procedures of both registries were enhanced to reduce time to registration. New abstract forms including detailed information on extent of disease, tumour size, spread and nodal involvement were adopted. All registered cases of breast cancer were followed-up to 2001 to assess their vital status. Hospital records were first reviewed. Treating doctors and the cases' families were contacted for complement of information.

In a pilot study we tested the feasibility and reliability of active collection of death certificates (for all causes of death) for linkage with the study cohort. Mortality rates computed from the information thus obtained were however unrealistically low and cancer was over-represented. This activity was therefore abandoned, and only cancer deaths continued to be recorded, as part of the usual routine of the cancer registries. Breast cancer cases and deaths identified during the follow-up period were linked with the master file (interviews and CBE results) and lists of eligible women (intervention and control areas) using a probabilistic record linkage software 'RECLINK'1.

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[1] RECLINK is a record linkage software developed at unit of Descriptive Epidemiology, International Agency for Research on Cancer, Lyon. The software performs probabilistic linkage

Uncertain matches were sorted out by the registries' directors after consultation of paper documents.

All matched cases were retained as incident if date of diagnosis recorded by the registries occurred after date of enrolment. This was defined as the date of interview/examination for women in the intervention cohort, and the mid-point of the intervention period (30 January 1997) for other women (listed in the electoral rolls, in either arm).

Data analysis. The main outcome measures are the number and cumulative incidence of breast cancers in the intervention and control cohorts identified by electoral rolls, and in the cohort of actually interviewed women. Since only one screening round was performed, sensitivity, specificity and predictive value were calculated using as gold standard the incident cases identified by the registries in two years from screening examination, including those diagnosed at the time of testing. Additional parameters describing the performance of the intervention are presented as absolute and relative frequencies, means and their standard deviations and 95% confidence limits (c.i.). Because of the large numbers of subjects involved, statistical testing was avoided when comparing cohorts. Confidence limits of proportions are based on the exact binomial distribution. Differences between proportions adjusted for age were tested by the Mantel-Haenzel procedure.

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between records from different sources using selected personal identifiers (names, date of birth, sex, address, tribe).

Results

Randomization. There were 101 HCs in each arm (intervention and control). The overall estimated number of people resident in the two arms was very similar, 1.82 million, as was the estimated proportion of deprived HCs in control (29%) and in intervention (29%) areas.

Population lists. We compared counts and age distributions of the population by study arm and municipality based on the census data, lists generated from electoral rolls and the questionnaires of interviewed women. Overall the three sources gave similar counts with differences between any two in any one municipality that were less than 5%.

Intervention. The results of the intervention after completion of the single round of examinations, and the newly diagnosed breast cancer cases in two years of follow-up are summarized in Table 1. The number of women interviewed and offered CBE was 151,168; 8% of these women refused to be examined. Three thousand four hundred and seventy-nine women (2.5% of those examined) were judged to have a lump and were referred to the project clinics. Of these, 1293 (37.2%) received further investigation, and complete diagnostic follow-up was achieved for 1220 women, 35% of those positive on screening.

One-thousand four hundred and seventy five women (42.4%) actively refused further investigation, even with a home visit, and 784 of the non-compliers (22.6%) were not traced, and were either reported by the neighbours, or assumed, to have moved away or died.

Among the 1220 women who completed diagnostic follow-up, 34 malignant cancers were detected; the presence of a lump was not confirmed in 563 (46.1%) and 623 (51.1%) were diagnosed as having benign breast disease.

Because of the poor compliance with follow-up of screen positive women, even with home visits, the active intervention was discontinued after completion of the first screening round in December 1997.

Comparison of characteristics of women accepting or refusing screening.

Table 2 shows some socio-demographic characteristics of the two groups as assessed at interview, women interviewed and examined, and women interviewed who refused CBE. The two groups were very similar in age, 44.8±8.2 years and 44.7±8.4 respectively, and were also of similar age at menarche, between 13.0 and 13.6 years, but differed for other variables. Refusers were one year older at their first full-term pregnancy and of higher socio-economic status than compliers (as shown by the proportion of women who attended college (18% *vs.* 12%) and the proportion illiterate (6% *vs.* 18%)), had a significantly greater income (medians were Pesos 7,000/month *vs* 4,500), were more often nulliparous (17% *vs.* 10%) and less likely to have had 5 or more children (25% *vs.* 33%). Thirteen percent of compliers declared using oral contraceptives and 21% reported other contraceptive methods. The corresponding percentages were 9% and 13% among refusers. Around 70% of the women in both groups had never had a cervical cytology test. Tobacco smoking and alcohol drinking are rare habits in this female

population, 8% of compliers were regular smokers and alcohol drinkers *vs.* 7% and 11% respectively of refusers.

Proportion positive by selected personal characteristics.

Among examined women the positivity rate decreased constantly with age from 2.9% in women below 40 years to 1.5% in women aged 60 or more (table 3). The percentage of women detected positive was higher in those with less than three pregnancies (3.3% *vs.* 2.2%) and among those who attended cervical screening (3.3% *vs.* 2.1%). The positivity rate was not consistently associated with the level of education and was higher in women reporting low income. It ranged from 1.1% to 6.0% in the 12 municipalities. Rates above the average were recorded in the more affluent areas of Makati (4.0%), Mandaluyong (6.0%) and Malabon (3.9%). The high rate of positives among women with missing information, in particular on education level, is an interviewer effect. In fact we observed an inverse association between total number of interviews and examinations performed per nurse and both their referral rate, and the rate of missing answers in their interviews. In other words the less experienced the poorer the performance.

Outcome of record linkage.

The file of the women interviewed was linked with the files of the eligible population listed in the electoral rolls. Only 19% of the women interviewed and examined in the intervention cohort could be linked with records of women in the electoral rolls (figure 1). The proportion of records matched varied significantly by municipality from 7% to 36%. The discrepancy reflects the high turnover of the resident population and variable accuracy in the maintenance of the lists. Assuming that the same bias affects electoral rolls

of the two randomised arms, this source provides suitable denominators for the comparison of the incidence in intervention and control arms.

Follow-up. After exclusion of cases whose incidence date preceded date of recruitment, there were 514 breast cancer cases, incident within 2 years of enrollment linked with records of women in the electoral rolls or in the intervention cohort (figure 1). The cumulative incidence (Inc.) of breast cancer was 11.6/10,000 women in the control arm, 9.7/10,000 in the intervention arm as identified by electoral rolls and 8.8/10,000 in the women invited for screening (interviewed cohort). All of the 133 cases identified among interviewed women had complied with CBE. Eighty of these had been judged negative on CBE (figure 2) corresponding to a cumulative incidence of 5.4 new cases per 10,000 screen-negative women. Fifty-three cases were detected among the 3,479 women who were screen-positive (152.3/10,000), 38 of which were detected through the intervention itself (311.5/10,000) although 4 were among women initially diagnosed with benign disease (33.7/10,000). Fifteen cases occurred among those women who did not complete the diagnostic process (84.0/10,000), of whom six were refusers (40.6/10,000) and 9 lost to follow-up (114.8/10,000). Thirty out of 38 screen-positive cases were diagnosed within 12 months of the first examination, only 4 were diagnosed later. Four malignant cases were diagnosed in 4 women positive at CBE who complied with clinical follow-up and were judged negative for malignancy (two by CBE performed by the specialist doctor and two by fine needle biopsy). Histologically confirmed malignant BC was diagnosed at least 12 months after screen-examination in all of them. Of the 15 cases identified among refusers 11 occurred within a

year and 4 later. The 80 cases diagnosed among screen-negative women were almost equally distributed between the two periods.

Test sensitivity. If we generously allow that every positive examination in a woman who eventually proved to have cancer (within 2 years of the test) is a true positive, then the sensitivity was 39.8% (53/133), the specificity 97.5% (134,833/138,259), and the positive predictive value 1.5% (53/3,479). However, only 34 cases were actually diagnosed through the intervention reducing sensitivity to 25.6% and positive predictive value to 1.0% (34/3,479).

Table 4 shows the distribution by age of clinical extent of the disease in the 34 cases diagnosed by the screening process and in all other cases identified in the examined cohort. These included 80 cases screen-negative, 15 lost to diagnostic follow-up or refusers and 4 among women diagnosed as having benign disease. None of the screen-detected cases had distant metastasis at presentation while 17% of the others had metastatic disease (p=0.032 two-sided test of the difference between the two proportions). The proportion of advanced cases increased with increasing age from 12% below 45 years to 27% at age 55+ years (test for trend, p=0.037). Two in three of the staged cases originally classified benign presented with distant metastasis.

Figure 3 shows the relative distribution and 95% c.i. by stage at presentation of the cases identified in the two arms (intervention and control) as defined by electoral rolls. The information was not available for 16% and 17% of the cases in intervention and control arm respectively. Based on the staged subgroups, the proportion of advanced cases (presenting distant metastasis at diagnosis) was 15% in both groups. In the intervention cohort 36% were

localized (95% c.l. 29%-43%) compared with 31% (95% c.l. 24%-38%) in the control cohort, all at the expense of regional involvement the frequency of which was 50% (95% c.l. 42%-57%) and 55% (95% c.l. 46%-61%) respectively. The confidence intervals largely overlapping indicate that the 5% difference between case and control groups are far from statistical significance.

Discussion

Breast cancer is a growing problem in developing countries. Increases in incidence and mortality are widespread and often more marked in younger generations of women[1]. In populations of South-Eastern Asia increases range from 1% to 3.6%[23,24,25,26]. Mortality of cancer cases and breast cancer cases in particular is unnecessarily high[8].   Known risk factors are linked to reproductive history and lifestyle and are hardly modifiable, rather they are likely to become more prevalent with economic development. In these circumstances, interest has tended to focus upon early diagnosis and treatment, as a means of reducing at least mortality [19,20,21].

The efficacy of breast self-examination as been formally tested in a randomised trial in Shanghai, China[22]. No significant reduction of breast cancer mortality in the intervention group was detected after 10 years of follow-up and the distributions of stage at diagnosis in screen and control groups were very similar. However, the small size of the lesions diagnosed in the control subjects in this trial (47 % $\leq$2 cm diameter, 48% node negative) suggests a high level of health-awareness in this special subset of

the Shanghai population, and may give little scope for improvement in outcome through early detection by BSE.

Clinical breast examination carried out by a trained examiner has many attractions. In programmes where it is combined with mammography, CBE finds fewer lesions but does detect some that had been missed by mammography. In general the differential is less for younger women[23]. In the CNBSS II trial of women ages 50-59, there was no significant difference in the efficacy of CBE and mammography[24]. CBE has been introduced as a single screening modality in Japan. There is some suggestion that, where coverage by such screening is high, breast cancer mortality rates have declined more than in other areas[25], although a case-control study was inconclusive[26]. Manpower requirements for a screening programme based on CBE would be expensive but in many developing countries these are generally easier to mobilize, than the technology required for mammography. Based on these arguments, it has even been suggested that CBE would be a more cost-effective alternative to screening women at high risk, in low-income countries27.

The trial in Manila was designed to assess whether a meaningful reduction in mortality from breast cancer could be achieved in a developing country using an inexpensive procedure and locally available resources, that is physical examination of the breast performed by nurses and midwives. The mortality reduction that was aimed for, among the women actually screened and followed-up, was 25%, that is a smaller effect than that of mammography which had been demonstrated in randomised controlled trials (RCT) settings to reduce mortality by about 30-35% among screened

women, and probably the minimum mortality reduction that would be worthwhile in any future programme. The Manila area was selected for the trial for several reasons, the relatively high incidence of breast cancer; the availability of treatment facilities (surgery, radiotherapy and systemic therapy are provided by both the public and private service); and the possibility to recruit a large number of qualified nurses to act as examiners.

The unexpected result that jeopardised the whole intervention was the unforeseen reticence of women found with abnormalities and informed of the implications to their life, to pursue diagnosis and treatment.   These problems had in fact been noted during a pilot phase. In the main study they were addressed from the beginning by provision of free transport and consultation. However, this tactic was not sufficient, and a programme of diagnostic home visits was introduced. Even this failed to raise compliance with diagnostic follow-up beyond 35%. The reasons can only be speculative at this stage but deserve *ad hoc* studies. One may think that women did not understand the implications of undergoing CBE. However, this is a relatively educated population and highly exposed to media messages. Alternative hypothesis are also possible. Lack of trust in the health system and in one's chances to be cured may discourage action. Such attitude is not in contrast with accepting screening. In a recent survey in the U.S., 60% of interviewed people reported they would wish to be examined for a cancer for which there is no hope of cure[28]. It is known that women attend for breast cancer screening in anticipation of a negative finding[29], and screening is not a stressful procedure for those with a negative mammography[30,31]. However, receipt of an abnormal result is associated with considerable psychiatric morbidity[32,33,34], and this may have played a role in the low level of

compliance. The decision not to undergo investigation was a positive one in most instances, and not related to logistical or financial barriers. It is known that patient's decision making is not always apparently rational. Misinformation, denial, overconfidence, distrust and confusion may all play a role[35].

The second major limitation highlighted by this study is the modest sensitivity of the screening test in the setting in which it was applied. Sensitivity and specificity of CBE have been measured in randomised trial of mammography and screening programmes, relative to new cases diagnosed within 12 months detected by either CBE or mammography and including interval cases. In these conditions the average sensitivity and specificity were 54% and 94% as estimated in the meta-analysis by Barton[37]. The sensitivity was higher in the Canadian trial in the control arm who did not receive mammography[38]. Sensitivity estimates are difficult to compare due to varying definitions of the reference gold standard in different studies. In our study the reference set included only cases that surfaced clinically within 12 or 24 months, the majority of which were relatively advanced (table 5). We would expect therefore an even lower estimate of the sensitivity had the cohort also been screened by mammography.

Our results reflect what might realistically be expected from CBE as a screening modality when applied by nursing personnel formally trained in the procedure but necessarily inexperienced. Clearly, if CBE is to be at all useful, a much greater effort in training and quality control of performance than was possible in the Manila trial will be required. But it is unlikely that this can be obtained from staff in primary health centres normally dealing with more

common diseases. One could envisage a new professional profile of health workers who specialise in the diagnosis and follow-up of cancer and are made available regularly in health centres.

This study has indicated additional problems relevant in the evaluation of future interventions. They include the feasibility of the long-term follow-up due to the high mobility of this population and the lack of up-to-date registers of the resident population. These are key aspects of the evaluation of randomised trials but were made unimportant in this study given its premature end.

Conclusion

We show that in the urban population of Manila serious logistic as well as psychological barriers to seeking medical attention for breast cancer persist. An occasional contact with unknown health workers has a minimal impact on health-beliefs and behaviours. In addition, the sensitivity of CBE performed by trained but inexperienced personnel is low. Yet, early diagnosis remains a high priority in order to improve the lamentable stage distribution that leads to premature death of a large number of cases.

Advocacy needs to be reinforced taking inspiration from the experience of high-risk countries[36] but bearing in mind the specific context where other diseases will continue to be of greater importance and governmental expenditure in health care is unlikely to increase substantially. Alternative organizational settings need to be devised and tested. Access to early diagnosis could be improved for instance by promoting detection of BC

among health operators in first level primary care services that interact with the population on a daily basis. Rotating breast clinics could be organised on a regular bases within health centres for primary care, to teach and encourage BSE and to provide opportunistic CBE performed by experienced personnel devoted to this task. The regular presence of specialised personnel could also help to raise awareness and trust.

In recent years research on means to improve cancer control when resources are limited has focused on the evaluation of low-cost screening procedures and this study is an example in this direction. The outcome of the Manila trial is a reminder however, that culturally-related health beliefs are a major obstacle to early diagnosis and that awareness and access need to be addressed in first place.

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Table 1.
Results of the single round of screening, and clinical outcome after 2 years of follow-up.

Number of women interviewed:	151,168	
Number of women examined:	138,392	(91.5%)
Number positive on screening:	3,479	(2.5%)

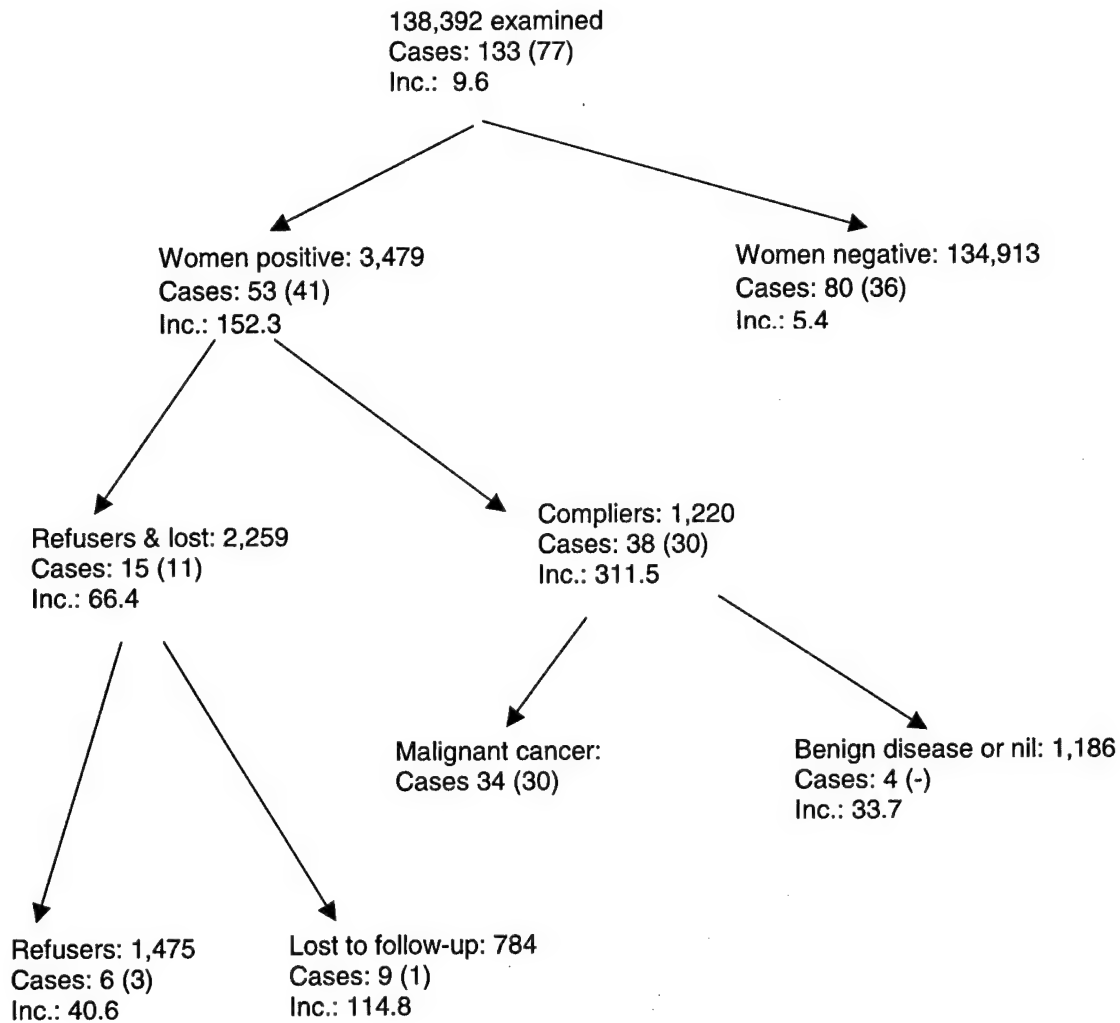| Women CBE-positive			Cancers diagnosed by screening
1,220		Completed diagnostic follow-up	34
	556	at project clinics	21
	73	at another clinic	1
	590	at project clinic after home visit	12
1,475		Refused or follow-up incomplete	
784		not traced	
3,479		TOTAL	

Table 2.
Comparison of characteristics of women examined and interviewed women who refused examination.

	compliers N=138,392	refusers N=12,776
age in years (mean±SD)	44.8 ± 8.2	44.7 ± 8.4
Illiterate (%)	18.0	6.2
attended college/university (%)	12.3	17.7
monthly income (pesos) mean±SD	5744 ± 5590	10806 ± 12023
Income/No. of cohabitants (pesos)	1556 ± 1713	2748 ± 3292
mean age at menarche	13.6 ± 1.7	13.4 ± 1.5
mean age at first full-term pregnancy	23.0 ± 4.5	24.1 ± 4.5
ever used any contraceptive method	20.8	13.1
nulliparous (%)	10.3	16.6
women with 5 or more children (%)	32.6	25.3
never had a PAP smear (%)	69.9	72.3
smokers (%)	7.7	6.5
drinkers (%)	7.8	11.2

Table 3.
Proportion positive women per 10,000 examined, by selected personal characteristics.

		No. positive	No. examined	Positives /10,000
All		3,483	138,392	
age	< 40	1,356	46,896	2.9
	40-49	1,443	53,459	2.7
	50-59	538	28,470	1.9
	60+	145	9,543	1.5
	unknown	1	24	4.2
education	max primary	925	59,803	1.5
	max secondary	997	50,221	2.0
	college+	312	17,072	1.8
	unknown	1,201	14,452	8.3
pap-test	ever	1,290	39,285	3.3
	never	2,017	96,789	2.1
	don't know	176	2,318	7.6
Full-term pregnancies	<3	1,302	39,777	3.3
	3+	1,920	87,562	2.2
	missing	261	11,053	2.4
Monthly income per No. of cohabitants	low	1,679	60,799	2.8
	high	1,031	57,998	1.8
	unknown	674	19,595	3.4

Figure 2. Number of women examined and breast cancer cases identified in the intervention cohort within two years of screening and cumulative incidence per 10,000 women, by screening outcome and time since CBE. In parentheses cases identified in the first year.

138,392 examined
Cases: 133 (77)
Inc.: 9.6

Women positive: 3,479
Cases: 53 (41)
Inc.: 152.3

Women negative: 134,913
Cases: 80 (36)
Inc.: 5.4

Refusers & lost: 2,259
Cases: 15 (11)
Inc.: 66.4

Compliers: 1,220
Cases: 38 (30)
Inc.: 311.5

Malignant cancer:
Cases 34 (30)

Benign disease or nil: 1,186
Cases: 4 (-)
Inc.: 33.7

Refusers: 1,475
Cases: 6 (3)
Inc.: 40.6

Lost to follow-up: 784
Cases: 9 (1)
Inc.: 114.8

Cancers actually detected by the screening programme:
   34/138,392 = 2.5/10,000

Total cancers found in women examined:
   53/138,392 = 3.8/10,000

Table 4.
Breast cancer cases that occurred among screened women, by stage at diagnosis and screening outcome. Numbers, percentages and 95% c.i.

	unknown	Localised	Regional	Distant	Total known stage
Age<45 years					
Screen-detected, No (%)	5 (50)	-	5 (100)	-	5
other cases[a],no.(%)	3 (10)	7	16 (62)	3 (12)[b]	26
Age 45-54 years					
Screen-detected, No (%)	6 (35)	2	10	-	12
other cases[a],no.(%)	5 (12)	6	22 (61)	8 (22)[b]	36
Age 55+ years					
Screen-detected, No (%)	4 (60)	-	2 (100)	-	2
other cases[a],no.(%)	7 (24)	4	12 (55)	6 (27)[b]	22
All ages					
Screen-detected, No (%)	15 (44)	2 (11)	17 (90)	- (0)[c]	19
other cases[a],no.(%)	15 (15)	17 (20)	50 (60)	17 (20)[c]	84

[a] Screen-negative or screen-positive lost to follow-up or screen-positive benign disease.
[b] Test for trend in the prevalence of advanced cases by age: p=0.037
[c] Difference in the prevalence of advanced cases, screen-detected *vs.* other cases: p=0.032.

Figure1. Follow-up to 1999. New cases of breast cancer identified in control (218) and intervention (211) arms as defined by electoral rolls. Of the new cases in the interviewed cohort (137), 48 were also linked with records in the electoral rolls. In brackets [] number screen-detected cases.

Control arm: 218
(188,063)

Intervention arm: 211
(216,884)

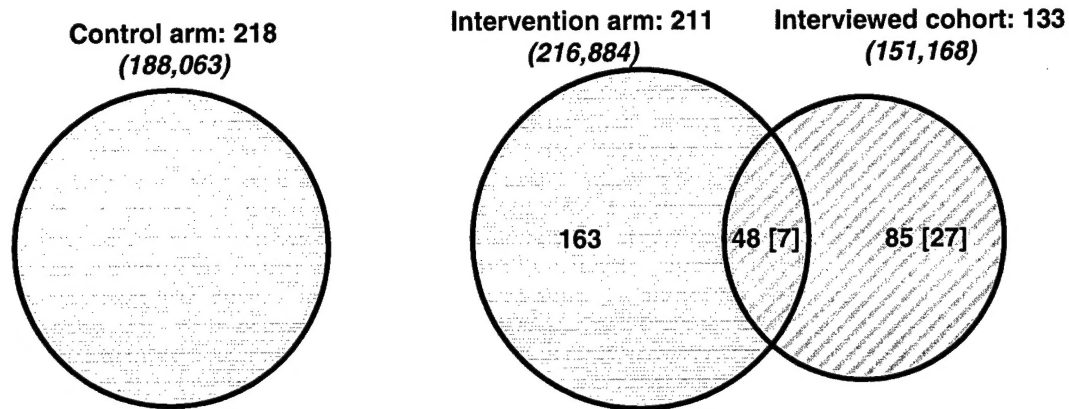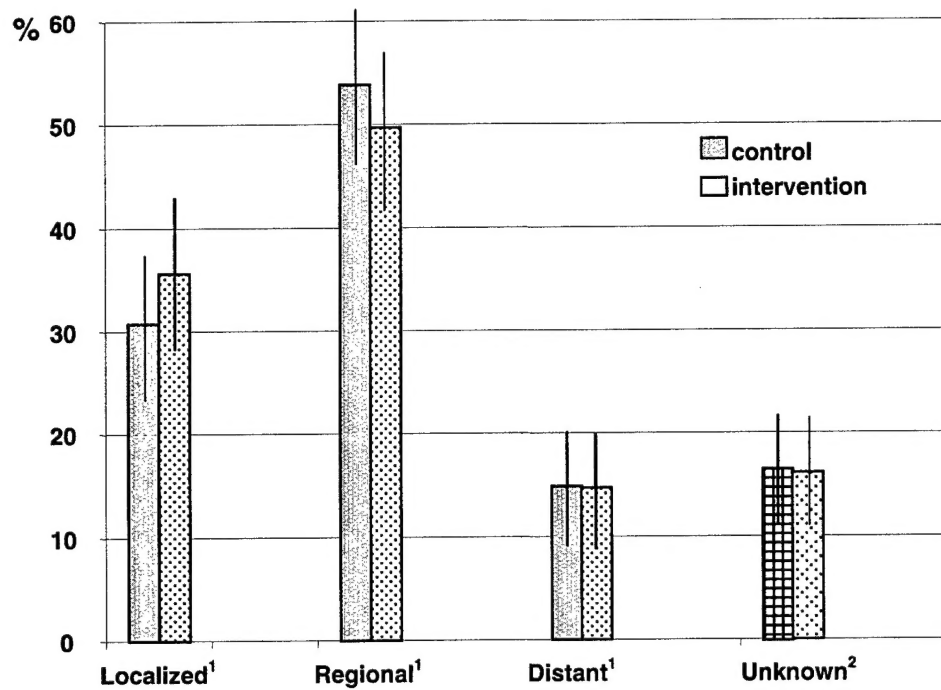**Interviewed cohort: 133**
(151,168)

163   48 [7]   85 [27]

Figure 3. Incident cases by stage in the two arms defined by electoral rolls.
Percent and 95% c.i. of 211 and 218 cases in intervention and control arm respectively.

[1] Proportion of all known stage.
[2] Proportion of all cases.

TREATMENT PRACTICES FOR BREAST CANCER IN MANILA
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Introduction Around 1995 the incidence of breast cancer in the female population of Manila was 57.4/100,000 (world standardised), the highest in Asia excluding Israel and even higher than in some areas of Southern Europe. Since early breast cancer can be treated effectively we conducted a descriptive study of the treatment regiments that are provided

Materials and Methods Source data were obtained from the data set of the PCS-Manila Cancer Registry. Breast cancer cases incident in 1991, 1994 and 1997 were selected. After exclusion of cases recorded on the basis of the death certificate only, and of those registered as metastatic at diagnosis (summary stage routinely recorded by the registry), we drew a random sample of 992 cases. An abstract form was prepared to collect information on diagnostic procedures, TNM stage, and treatments received separated into surgery, radiotherapy, adjuvant chemo and hormonal therapy. Dates of first administration and the names of the treating doctors were also abstracted. Medical records of all the cases were reviewed first. Treating doctors were then contacted by one of the authors (AL) to obtain complementary information, particulary on the use of adjuvant therapies that are often administered in private practices.

Results The 992 cases were almost equally distributed in the three incident years of interest (301, 342 and 349 respectively). Forty cases were advanced at diagnosis and therefore excluded, and no clinical information could be traced for 207 (21%) leaving a total of 745 cases, of whom 98% were microscopically verified.
Staging. 99% of the cases received a chest x-ray and less than 4% were also examined by computerised tomography, liver ultrasound or bone scan. Stage was not assessed for 5% of the cases. Ten percent were stage I; 31%, IIA; 29%, IIB; 26% stage III. This pattern was constant in the three years considered.
Treatment. 97% of the cases received radical mastectomy irrespective of stage at presentation. Only 17% of the cases received radiotherapy and the proportion increased steadly from 8% in stage I to 27% in stage IIIB. On average 53% received adjuvant chemotherapy; the proportion treated was higher in women below 50 years of age (55%) and declined to 35% in cases aged 60 or more. There was not a systematic association with stage at presentation.
Finally, tamoxifen treatment was administered to 51% of the cases with a significant inverse association with age (57% of cases below 50 years were treated *vs.* 42% in age group 60+ years). We also observed a trend towards an increasing proportion of treated cases with stage becoming more serious: 39% of stage I *vs.*58% in stage 3B. The use of hormonal treatment almost doubled between 1991 and 1994 and remained stable thereafter.

Conclusions. We have shown in previous studies that still too many cases of breast cancer present at diagnosis with advanced disease. With this work we show that standard treatment for non-metastatic cases is sub-optimal. In a country with limited resources to control cancer, interventions to improve and generalise access to optimal treatment for tumours that are potentially curable, would be cost-effective and should be of high priority.